II

INSULIN IN DISCOVERY AND USE

THE discovery and use of insulin for the treatment of diabetes is a recent outstanding achievement of science. In recognition of the great service thus rendered to mankind, the discoverer, Dr. F. G. Banting, received the Nobel Prize in Medicine for 1922. Such recognition alone signifies that the scientific research in this field carried on during the last few years by Dr. Banting and his associates at the University of Toronto is considered by competent authorities to be of fundamental importance to the progress of medical science.

Before taking up the main part of my thesis on the discovery and use of insulin, it might be well to discuss briefly the fundamental causes and physiological aspects of diabetes, in order to understand more clearly the source of the discovery of insulin and the reasons for its use; for the discovery of insulin was by no means accidental, but decidedly the result of a direct search by a man who knew just what he was looking for, and approximately where to find it.

Diabetes is classified as one of the diseases of metabolism, that is, a disease resulting from an improper diet or the failure of the digestive system to utilize with the greatest efficiency the common foodstuffs of a normal diet. One authority defines diabetes very simply as "a disease in which the metabolism of carbohydrates, together with that of the fats, is disturbed." This simply means that the digestive mechanism of a diabetic is for some reason unable to utilize fully the chemical compounds that constitute by far the largest part of our foodstuffs. Other more or less familiar types of diseases of metabolism are scurvy, beri-beri, and pellagra in adults, and rickets in children. These diseases differ from diabetes in that certain vitally important substances known as vitamines are lacking in the diet, whereas the cause of diabetes is not due to a deficiency of any certain ingredients in the diet, but rather to a deficiency of some necessary substance contained in the body.

Since, according to the definition, diabetes is a disease in which the metabolism of carbohydrates and fats is upset, let us consider first the normal path followed by the carbohydrates and fats in the animal body.

The starches contained in our foodstuffs, on passing from the mouth to the stomach and then to the intestine, are decomposed into smaller and less complicated substances known as the simple sugars. These simple sugars, three in number, are then absorbed from the intestine by the venous blood stream, and carried directly to the liver, where, by some unknown process, these three sugars are converted into one sugar known as glucose, or sometimes called dextrose. Therefore, at this point, the starches of the diet are present as the one substance. A certain amount of the glucose then passes from the liver into the main blood-stream to maintain a constant supply of about 0.1 per cent., the rest remains stored in the liver in an easily available form for future use. The blood now circulates through the muscular tissue of the body, where the glucose is burned to carbon dioxide and water, energy being liberated in this process. This is the path, briefly, of the fate of carbohydrates in the metabolic processes of the individual in normal health.

In the diabetic, however, the process of carbohydrate metabolism follows the normal path as outlined, up to the point only where the glucose leaves the liver in passing into the main blood-stream. The glucose now contained in the blood-stream is not completely burned to carbon dioxide and water as takes place normally; on the contrary, some glucose remains in the blood-stream. With the consumption of more carbohydrates in the diet, more and more glucose is eventually poured into the blood, until at last a certain percentage of glucose is reached which may be two to three times the concentration normally found. The actual concentration of glucose reached in the blood of different diabetic patients varies within certain limits, depending on the individual. Finally, the concentration of the glucose in the blood rises to such an extent that no more can be absorbed. At this point, the kidneys begin to eliminate the glucose by absorbing it from the blood, and excreting it in the urine. The presence of glucose in the urine, therefore, is one of the danger signals of the onset of diabetes. However, the presence of glucose in the urine does not necessarily indicate diabetes, for after a meal consisting of a heavy carbohydate diet, and after certain violent emotional conditions, glucose is often found in the urine. This condition does not last very long, and the glucose soon disappears in the normal person; in the diabetic, however, glucose appears persistently in the urine.

It has been known for a long time that the combustion of glucose in the blood is controlled by four glands in the body, namely, the adrenal, thyroid, pituitary, and pancreatic glands. Of these, the pancreas has been shown to have the greatest effect. The pancreas is a small gland located just under the stomach. It is composed of two parts, one of which secretes the pancreatic juice into the intestine, and the other part which is composed mainly of certain cells known as the Islands of Langerhans. It has been known for a long time that the function of these islands is to secrete into the blood a substance in the presence of which combustion of glucose into carbon dioxide and water takes place. Therefore, it is the failure of these islands to function properly which causes the glucose to remain in the blood unburned, and thus produces diabetes. The fundamental cause of diabetes is, therefore, the failure of the pancreas to function properly, the metabolic cause being only of secondary importance.

When glucose cannot be properly burned, the metabolism of fats is also upset. The normal digestion of fats follows a somewhat similar path to that taken by the carbohydrates. In passing from the mouth into the stomach, and thence into the intestine, the fats are decomposed into two products, namely, the fatty acids and glycerine. These products are then absorbed from the intestine by the lymphatic system, and soon find their way into the main blood-stream. Here, the fatty acids and glycerine are burned to carbon dioxide and water in a way similar to the sugar combustion, also supplying energy to the muscular tissue.

In a diabetic patient, however, these fatty acids are not completely burned to carbon dioxide and water, but stop short of the normal combustion, being only partly burned. These partly burned products are known as the acetone bodies. Prior to 1914 this failure of incomplete fat metabolism was not generally recognized as one of the symptoms of diabetes, and furthermore, it was not until several years after this time that the reason for incomplete fat metabolism accompanying incomplete carbohydrate metabolism was known. The reason for this complication is this: in order for the fatty acids to be completely burned to carbon dioxide and water, the glucose in the blood must also be completely burned. Or, as one authority cleverly puts it, "Fats burn in the flames produced by the burning of the sugar." This relationship between these two processes is an experimental fact, but as yet we have no satisfactory explanation of the fact. These partially burned fatty acids, the acetone bodies, remain in the blood-stream, and are ultimately removed by the kidneys and excreted in the urine. Therefore, the onset of diabetes is recognized primarily by the continued presence of glucose and the acetone bodies in the urine. Of course other physical symptoms appear, such as loss of weight, thirst, and general weakness.

Here let me summarize the foregoing facts. From a study of the chemical and physiological causes of diabetes, we can say briefly:

First, the primary cause of the onset of diabetes is due to the failure of the Islands of Langerhans, located in the pancreas, to secrete into the blood a certain substance which is necessary for the complete combustion of the normal amount of glucose in the blood.

Second, due to this fact, the amount of glucose in the blood rises considerably above the normal 0.1 per cent., until a certain concentration known as the "leak-point" is reached. The excess glucose now overflows through the kidneys, and is eliminated in the urine.

Third, attending the failure of complete sugar metabolism and complicating this state, is the incomplete metabolism of the fats, due to the fact that the second process depends wholly on the first. This results in the formation of the acetone bodies in the blood, and their subsequent elimination in the urine.

Since the present method of treatment of diabetes with insulin depends to a great extent on the older methods, it might be well to consider these briefly. Prior to 1914, diabetic patients were overfed, all cases being treated with a low carbohydrate and a high protein-fat diet. This was before the medical profession recognized the fact that fats played a minor part in the disease. The giving of diets of large calorific value was encouraged, and fats and fatty foods were given to an enormous extent. To guard against coma, one of the complications of diabetes, gradual restrictions of the diet were advised, and sodium bicarbonate (ordinary baking soda) was employed in large doses. The value of fasting and of giving limited calorific diets was not grasped by the medical profession in general until late in the year 1914, when, in consequence of Allen's investigations, the principle of fasting and under-nutrition was introduced. Even then, it was not until late in the year 1915 that this practice became the general rule. This change in the method of treatment profoundly affected the metabolism of diabetics. Also, at this time, fats were recognized to be a source of complication, as I have already pointed out; so that they were eliminated from the diet.

The dietetic treatment used in general to-day is essentially that advised by Allen, namely periods of fasting, interspersed with periods of under-nutrition, closely following the course of the metabolic processes with urine analyses for sugar and the acetone bodies. No commonly known drug has any influence on the metabolism of sugar. Purgatives and general tonics for the health are sometimes used.

Diabetes is not in itself the actual cause of death, rather it is the complications arising from severe cases of diabetes that result fatally. Of the several known types of complications that may follow, only two are prevalent enough to discuss. The most common complication is that of coma. Before the treatment of diabetes was fully understood, this was the frequent termination of the disease. Prior to 1914 Allen reports that eight-six per cent. of diabetic patients died in coma. With a better understanding of the method of treatment, that is dietetic treatment alone, this rate dropped steadily, until, in 1919, only fifty-two per cent. died of this complication. Coma is now the result only in untreated, very severe, and long-standing cases, wherein the choice lies between death from under-nutrition or coma from overfeeding. Of course, I have not as yet touched upon the prevention of coma by the use of insulin, but this will be presented later. Pneumonia is responsible for the death of a small percentage of diabetic patients. During the period 1908-1917, the mortality rate was about eight per cent. Other complications are much smaller in extent.

We have now considered the chemical and physiological causes of diabetes, the fatal complications resulting from it, and the less recent methods of dietetic treatment. Up to the year 1922, the only method of treatment used was that from a dietetic standpoint. In this year, with the discovery of insulin by Banting and his associates, the old method of treatment changed. Before taking up this phase of the value of insulin, let us first consider the early investigations which led to its discovery. During the period, 1885-1900, several German and French investigators showed conclusively that the removal of the pancreas from dogs was accompanied by the appearance of symptoms of diabetes. The content of blood-sugar rose above the normal level, and sugar was also excreted in the urine. This was the first time that the all-important relation between the active functioning of the pancreas and the combustion of sugar was shown. In 1909, Zuelzer, a German investigator, attempted to extract the active principle from the pancreas. His methods of extraction were poor, but he did get an extract which produced some slight effects on the combustion of the blood-sugar. He administered this extract to several of his patients with but partial success, and soon abandoned the practice, since his extract was quite toxic, and the good results produced were offset by the toxic effects. In the light of our present knowledge of the isolation of insulin, Zuelzer's method was sound, but his investigations were not comprehensive nor conclusive enough for him to receive the credit for the discovery of insulin. E. L. Scott, an American, working at the University of Chicago in 1912, also attempted to isolate the active principle from the pancreas. His work was likewise unproductive of any startling results, yet his method of extraction was quite similar to that later employed by Banting with great success. In 1913, two other investigators made extracts of the pancreas and injected their preparation into diabetic dogs with moderate success. They, also, failed to carry their investigations sufficiently far before discontinuing their work.

Such was the state of affairs in November, 1920, when Dr. Banting happened upon some passages in medical literature which suggested to his open mind a rational method for the isolation of this elusive substance. The facts upon which he based his subsequent investigations were these: in 1890, Langerhans found from a minute observation of the pancreas, that there were present in the main part of the gland certain very small cells which had hitherto escaped notice. These cells seemed to him to have a different cellular structure, and to have a different function from the other cells of the gland. It was shown that these islands did have a different function when it was observed that in the case of patients dying from diabetes these Islands of Langerhans were found to be destroyed. An experiment had also confirmed this fact, for when the duct leading out of the gland was tied, and the gland allowed to degenerate as all unused organs do, the Islands of Langerhans remained unaffected, and the metabolism of glucose was not interfered with in any way.

Dr. Banting put a great deal of thought during the next six months on developing a suitable method for the isolation of this active principle from the pancreas. He studied very carefully the methods used by other men and the reasons for their failure. Finally he hit upon the following plan which he thought could be carried out to a successful result. Other investigators had simply extracted the active principle from the fresh organ. Their extracts had shown signs of containing some of the desired active principle, in that they produced some of the desired effects. But their extracts were very weak, and they were also toxic. Therefore, some other substance had simultaneously been extracted which destroyed the desired active principle. If this view be correct, Banting inquired, why not shut off the outlet of the pancreas in dogs, allow the gland to degenerate without injuring the Islands of Langerhans, as had been shown to be possible, and then extract the active principle from the islands after the rest of the pancreas has disappeared.

With his plan of attack thus worked out, he dropped his professional practice in London, Ontario, and went to the University at Toronto, where he talked to Professor J. J. R. McLeod, a noted physiologist and an authority in the field of metabolism. Professor McLeod agreed that Banting's plan was feasible, and gave him the necessary equipment and help to carry on his investigation, and assigned Mr. C. H. Best to work with him.

Several young dogs were obtained, and the pancreatic duct leading to the intestine was tied off. Ten weeks later, after the gland had completely degenerated, the dog was killed and the pancreas removed. This pancreas was then extracted with suitable liquids, and the liquid extract injected into dogs who were suffering from diabetes. The results confirmed Banting's hypothesis. The blood-sugar content immediately decreased. Other dogs were taken and their pancreatic glands removed. These dogs developed very severe cases of diabetes, but were kept alive indefinitely by regular daily injections of insulin. Without the constant injection of insulin the dogs quickly died.

Shortly after this Banting and Best prepared insulin from the pancreas of beeves. This extract was more powerful than the first one obtained, and was also less toxic, in that it produced less local irritation after the injection. This extract was not only tried on diabetic dogs, but was also tried on diabetic patients in the hospitals of Toronto. A decrease in the blood-sugar concentration, and the disappearance of sugar in the urine resulted in all cases. There was also some slight local irritation encountered in some of the cases, due to the presence of foreign proteins in the extract as impurities. The noteworthy result from this last method of preparation was this: it gave evidence that insulin could be prepared from a readily available source, namely from the beef pancreas obtained from our large stockyards.

With this fact as an incentive, an enormous amount of work was carried out by the investigators at Toronto to determine the best and cheapest method for preparing extracts of insulin. A half-dozen or more different methods of extraction were tried, using both hot and cold water, alcohol, benzoic acid, and other substances. Varying degrees of success were attained. Numerous variations in the physical conditions attending the operations were tried, all with the sole idea of producing insulin in the largest quantities possible and in the highest state of purity.

The method now used and controlled by the Toronto group, is a combination of the best points developed in the many variations attempted. Fresh pancreatic glands are obtained from beeves, and as much as possible of the attendant fat and connective tissue are removed. They are then ground in an ordinary meat chopper, placed in large vats and covered with ordinary grain alcohol. After a short time, the alcohol has extracted the insulin from the glands. The alcohol is next separated from the residue by filtration, and the alcoholic extract concentrated to a smaller volume. Ether is then added, causing the insulin to precipitate out as a fine white powder which is separated from the liquor, and dried. This white powder is then redissolved in sterile water, containing a slight amount of acid, and is used in this condition for medical work. This, of course, is a very brief outline of the essential points of the process which is much more detailed than I have indicated.

In any type of commercial manufacture, it is always the aim of the producer to get the maximum amount of the desired product from the smallest amount of initial material. So it is with the preparation of insulin. In April, 1922, the Toronto laboratories were able to get but fifteen units of insulin from two pounds of beef pancreas. Due to the various improvements in their methods, they have increased the yield to four hundred units from two pounds of pancreas. These latter figures are for July, 1923. Since that time, they have no doubt increased these figures considerably. The Toronto laboratories have done a great deal of work on the extraction of insulin from pork pancreas. This type of pancreas furnishes a relatively larger amount of insulin per pound than the beef pancreas, but the greater difficulty in handling it, with its increased cost, offsets the advantage of the higher yield.

As is always the case with the discovery of any new substance of value, everybody starts looking for the same thing in various other sources. A Dallas physician reports the isolation of an insulin-like substance from yeast. Dr. Collip, one of Banting's co-workers, has shown that insulin can be extracted from certain types of clams. Other animal sources, such as certain types of fish, the liver, spleen, thymus and thyroid glands of different animals and man, also give evidence of the presence of an insulin-like substance. The plant kingdom likewise, for instance, lettuce and onion and beet tops, have furnished insulin-like substances of slight importance. These, however, have yet to be thoroughly investigated.

With the preparation and use of insulin past the first experimental stage, it was the desire of the Toronto investigators to place this drug on the market as soon as possible. It was obviously impossible to manufacture in the little laboratories at the University of Toronto, insulin in large enough quantities to alleviate the suffering of all the diabetics in Canada and this country. The Toronto group also realized that to throw into the market the plans for the preparation of so valuable and important a drug as insulin would cause a great deal of unnecessary confusion and danger. They, therefore, appointed the Connaught Laboratories at Toronto to be the sole manufacturers of insulin for the Dominion. Banting and his co-workers formed themselves into a body, now known as the Insulin Committee, with direct control over its manufacture. The Connaught Laboratories have recently received from the Canadian Government an appropriation of twenty-five thousand dollars to be used in buying the necessary equipment for the preparation of insulin.

To supply the American demand, the Insulin Committee after careful consideration decided to invite representatives of the Eli Lilly Company, of Indianapolis, to come to Toronto to discuss the question of manufacture in this country. As a result of this conference an agreement was entered into whereby the Eli Lilly Company was granted an exclusive license in the United States for the manufacture of insulin, for an experimental period set provisionally at one year, under the following conditions:

First, that the firm use all of its available facilities and personnel for the manufacture of the product, and pay all expenses entailed in its manufacture on a large scale in their plant.

Second, that the firm submit samples of their product to the University of Toronto for approval before distribution to physicians for use on patients.

Third, that the approved product be distributed either free or at cost price only, to such physicians as may be chosen in consultation with the University of Toronto.

In consideration of the acceptance of these conditions by the Eli Lilly Company, on May 31st, 1922, all known details of the method of manufacture were given to the firm, and large scale production was immediately started.

The Insulin Committee showed commendable foresight by keeping direct control of the manufacture and standardization of this drug, for, as always follows in the wake of the introduction of a new drug, other manufacturing companies have been exploiting utterly worthless preparations which they "guaranteed to be just as good". The Eli Lilly Company product appears on the market as "Iletin". It comes in five cubic-centimeter vials of two different strengths. The weaker solution contains ten units per cubic-centimeter, and the stronger solution contains twenty units per cubic-centimeter. This latter solution of one hundred units sells at two dollars per vial, which is two cents a unit, a remarkably cheap price for so valuable a drug.

Since entering into the agreement with the Eli Lilly Company, the Insulin Committee has made similar arrangements with several European countries. England, Germany, and the Scandinavian countries are now producing insulin for their own respective use under the direct control of the Toronto group. In Denmark, in particular, large quantities of insulin are being produced, the highly developed swine industry of that country providing a fertile source for the production of the drug from the pork pancreas. Extraction of insulin from the pork pancreas had been attempted in Canada, but the process was discarded as impracticable; investigators in Denmark, however, have overcome the obstacles to this method, and are now making a very pure product.

I have already stated that the Insulin Committee also controls the standardization of insulin solutions. This is a very important factor in its use. Due to the fact that insulin is a chemical compound of unknown composition and structure, it cannot be analysed by any of the common chemical methods. Resort must therefore be had to a biological method of standardization. The insulin unit is defined as "one-third the amount which lowers the percentage of blood-sugar in a normal rabbit weighing 2 kg. (i.e. approximately four pounds), starved for twenty-four hours, to 0.045 of a per cent. in three hours." This means that a normal rabbit weighing approximately four pounds is starved for a period of twenty-four hours; the insulin solution is then injected, and three hours later the sugar content of the rabbit's blood is determined. From this datum, the exact strength of the insulin solution is calculated and the solution properly diluted or concentrated to meet the specific requirements of the set standards. Every individual quantity of insulin is thus standardized before it is put on the market for clinical use, and the medical profession is accordingly assured of successful results in its application to diabetic patients.

In spite of the great amount of research work done on insulin, its chemical structure still remains unknown. It is a white powder, containing carbon, hydrogen, oxygen, nitrogen, and possibly sulphur. It appears to be a protein, or at least protein-like in its composition. Its solution responds to many characteristic protein tests, for example, it gives a positive biuret test, a very characteristic test for all proteins. The dry substance is very soluble in water, and can be thrown out of water solution by shaking with charcoal. Finally, it is entirely inactivated by the protein-splitting enzymes, pepsin and trypsin, which occur in the stomach and in the intestine. These and other true protein characteristics are shown by insulin, so that the general opinion is that this substance is a protein of the albumin or globulin type. If insulin is a protein, the hope that chemists will ever be able to synthesize it is very small. It will probably prove impossible even to determine its chemical structure. The chemical structures of the well-known common proteins have never been determined, and no protein has been made synthetically in the laboratory. Insulin, in this respect, is quite different from our other naturally occurring drugs, such as adrenalin for instance, which after its discovery in the adrenal gland was proven to have a definite chemical structure, and is now made synthetically in large quantities.

It has been shown conclusively by the Toronto group and others that the injection of insulin into either the normal or the diabetic animal causes a decrease in the percentage of glucose in the blood. This disappearance may be accounted for in one of two possible ways:

First, the presence of insulin may cause the glucose to change its form or chemical constitution in such a way that it no longer reacts to the methods of blood-sugar analysis which are used.

Second, the presence of insulin may promote the combustion of glucose to carbon dioxide and water, as takes place in the normal animal.

No evidence has been found in support of the former assumption, but abundant experimental data have been obtained to confirm the latter statement. One method of determining and following the combustion of glucose, is to compare the amounts of oxygen consumed and of carbon dioxide evolved. Chemical laws show that for a given quantity of oxygen consumed in the combustion of glucose, there is an equivalent amount of carbon dioxide liberated, in accordance with the following equation:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O.$$

The ratio $6CO_2/6O_2$ is called the "Respiratory Quotient." If, as appears from the chemical equation, for every given amount of oxygen consumed there is an equivalent amount of carbon dioxide liberated, this ratio will be unity. The respiratory quotient of a normal person is practically unity, which means that the amount of CO_2 and O_2 are equal, thus showing that all the sugar is completely burned.

In a diabetic, however, the amount of CO_2 given off is less than the amount of O_2 consumed, so that the respiratory quotient becomes less than one. After an injection of insulin into a diabetic, the respiratory quotient value increases until in some cases it may even reach the normal value of unity. In all cases, however, the value of the respiratory quotient rises, which is direct evidence that insulin actually controls the combustion of the glucose in the blood.

In the light of our earlier discussion of the chemical and physiological causes of diabetes, one would expect a decrease in the acetone bodies to follow an injection of insulin. This is indeed what happens. By a continual use of insulin the acetone bodies are eliminated from the urine. This fact indicates again that insulin causes the complete combustion of the glucose.

It has been shown also that not only does insulin cause a decrease in the sugar content of the blood of a diabetic, but it also decreases a high sugar content due to other causes. For example, after anæsthetization with ether, or in asphyxia, the content of blood-sugar is abnormally high. A small injection of insulin promptly restores the glucose concentration to normal. In other words, valuable uses for insulin may be found other than that purely for the treatment of diabetes.

The actual method or mechanism by which insulin promotes the combustion of sugar in the blood is unknown.

It is fairly well established that the body tissues have some fundamental part in the reaction. This is shown by the following experiment: if the blood of a rabbit is removed and placed in a test-tube, and a solution of insulin added to it, the sugar is not burned. Also, if the solution of insulin is injected into the animal, and then a sample of his blood is quickly removed and placed in a test-tube, again no lowering of sugar content is detected. It is evident, therefore, that insulin is only active when it is present in the blood and in contact with the muscular tissues of the body.

There is another peculiarity of the action of insulin: it causes the combustion of no other simple sugar except glucose. We have a number of simple sugars resulting from the decomposition of starches in our foods. But, as has been noted in an earlier paragraph, these simple sugars in passing through the liver were changed to the one sugar, glucose. The liver, therefore, aids the subsequent action of insulin by forming the only sugar which insulin has any action upon. This coöperation between the liver and the pancreas is one of the many instances where two organs, seemingly with no connection to each other, are nevertheless closely related in the body processes.

Insulin cannot be regarded as a cure for diabetes in the usual sense of the word, but it enables the diabetic patient to utilize carbohydrates in the normal manner, thus giving his own pancreas a chance to regain its normal strength and vitality. Whether or not the use of insulin over a considerable period of time will give the pancreas the necessary chance to recuperate and thus function properly again, is a debated question, unanswerable at the present time because the general practice of insulin treatment is so very recent. It is entirely possible that in mild cases of diabetes a constant use of insulin may allow this to take place, and the patient may eventually be cured. In very severe cases it is probable that the pancreas has degenerated to such an extent as to be incapable of rejuvenation.

Insulin treatment cannot replace dietetic treatment. Where insulin is used, however, the calorific value of the diet may be much greater than it could be without its use. Roughly, the minimum calorific value of the diet for an individual at rest is fifteen calories per pound body weight. With the use of insulin, even in quite severe cases, the calorific value may be increased to such an extent that the patient may resume work.

The most brilliant results with insulin have been in the treatment of diabetic coma. When the patient is in this condition, large doses of insulin, from fifty to a hundred units, combined with an adequate amount of pure glucose, are injected directly into the blood-stream. In all cases of coma reported by the Toronto group, which have not been complicated by other factors, the patient's life has been saved by this treatment.

Up to the time of the discovery of insulin it was fatal to perform a surgical operation on a diabetic patient, due to the great increase in the blood-sugar content caused by the use of a general anæsthetic like ether. Now, surgery may be resorted to with comparative safety if the patient is given a large dose of insulin before administering the anæsthetic.

Except in very severe cases of diabetes, or in diabetic coma, the patient is taught to take care of his own daily insulin injection and his diet, as it is obviously impossible for the physician to be present to administer to the patient every dose of insulin required by him during the day. After diabetes is detected the patient is placed in a hospital where his diet is carefully balanced for him, and the daily injections of insulin given. His case is carefully studied, and he is taught the nature of his ailment and how to care for himself. The patient is generally kept in the hospital from two to four weeks, during which time the best diet and the proper dosage of insulin are determined for his individual case. He is then discharged and is now able to care for his own diet and to administer his own insulin dosage under the supervision of his physician. Several authorities on the treatment of diabetes have stated that comparatively little trouble has been experienced by the medical profession in allowing their patients to look after their own welfare.

Most of the mild cases require from ten to twenty units of insulin daily. At two cents a unit, this is a remarkably small sum to be expended for the comfort and pleasure which diabetics may enjoy in eating a wholesome and appetizing meal without fear of the results. Insulin is injected subcutaneously with a hypodermic needle, either one, two, or three times daily in definite relation to the meals. Best results are obtained if the injection is made from one-quarter to one-half hour before meal-time. The effect of a dose of insulin lasts, in general, about six hours, which insures the complete combustion of the carbohydrates of the diet during the periods between meals. It is unfortunate that insulin cannot be taken orally, for this method would eliminate the use of hypodermic injection. The nature of the drug prohibits oral administration, since it is protein in character, and would be inactivated by the protein-splitting enzymes of the stomach and intestine before it had a chance to function in the blood. Other methods of administration have been tried with negative results.

There is one grave danger liable to result from insulin treatment. An overdose of insulin will cause the blood-sugar content to drop considerably below the normal level of 0.1 per cent. When the sugar content falls to 0.06 or 0.07 per cent. the patient suddenly feels very weak and restless. On further decrease of the sugar, intense sweating, delirium, unconsciousness, and even death may follow. This condition may be quickly remedied by the administration of some form of carbohydrate food. In the early stages of this condition, relief may be obtained by administering cane sugar or corn syrup by mouth. If the patient is delirious or unconscious, pure glucose must be injected directly into the blood stream in order to save his life.

Due to the fact that the use of insulin in modern medicine is very recent, many of our leading universities and medical schools have started courses in the use of insulin for the practising physician, which are being well attended. Continued research on the preparation, action, and chemical composition of insulin is being carried on, especially at the University of Toronto, and the Medical School of St. Louis. It is estimated that there are some eighteen thousand persons in the United States alone that are now taking insulin treatment.

The brightest spot in the whole story of insulin is the attitude that Dr. Banting and his associates took toward the giving of insulin to the world. Had they been mercenary men, they could have made unlimited wealth by selling their patents or by selling their product at a high price. But they were not mercenary men, and refusing to entertain any idea of material gain to themselves, they arranged (in the manner outlined above) for the production and distribution of insulin at cost price. It would seem therefore, to be all the more appropriate that these men should have received the award of the Nobel Prize in Medicine for 1922, and the sum of forty thousand dollars which accompanies the award. Moreover, while the Nobel prize was originally awarded to Drs. Banting and McLeod, these gentlemen have generously shared both the honour and the money with their associates, Dr. Collip and Mr. Best. In the meantime the Canadian Government has provided in its civil list an annuity of seven thousand five hundred dollars a year for Dr. Banting, while the Ontario provincial government has made an appropriation of ten thousand dollars for the Banting-Best Chair for Medical Research, of which Dr. Banting is the first occupant.

Dr. Banting is thirty-two years old. He was born and raised in Ontario, and graduated from the medical school of the University of Toronto. He served overseas during the war as battalion doctor with the rank of captain, and was awarded the Military Cross for bravery.

This is a very brief outline of the discovery and use of insulin. I have endeavored to present some of the peculiarities of diabetes, both from a chemical and a physiological standpoint; the events leading to the discovery and preparation of insulin; and finally, some aspects of its use by the medical profession. In conclusion, I desire to thank the Insulin Committee of Toronto for so kindly sending me some of the information and data contained in this paper.

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